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Urological Outcome after Fetal Spina Bifida Repair: Data from the Zurich Cohort

Mazzone, Luca ; Hölscher, Alice Catherine ; Moehrlen, Ueli ; Gobet, Rita ; Meuli, Martin ; Horst, Maya

Abstract: INTRODUCTION Neurogenic lower urinary tract dysfunction (NLUTD) represents a severe burden for patients with open spina bifida (OSB). The effect of fetal OSB repair on the urological outcome remains unclear, as controversial data exist. The aim of this study was to further increment existing outcome data and to demonstrate that our earlier published positive preliminary results are not erratic. METHODS Data from standardized urological follow-up appointments of patients with fetal OSB repair operated at our center were analyzed. Data were obtained from urodynamic studies (UDSs) and radiologic exams performed in the newborn (gestational age 37-39 weeks), at ages of 6, 12, 18, and 24 months, and then at yearly intervals. RESULTS Of 82 patients (mean age 2.6 years, range 6 months to 7 years), 26 (32%) had a normal bladder function as demonstrated by UDSs. Of the 56 (68%) patients with NLUTD, 29 (51%) patients showed initially a normal UDS, but developed NLUTD in the follow-up, 19 (66%) of them spontaneously and another 10 (34%) in association with growth and development, or surgery of inclusion cysts. Radiologic abnormalities (upper tract dilatation and vesico-uretero-renal reflux) were seen in 15%, mainly patients with NLUTD. CONCLUSION Our results add an important set of information to the existing body of evidence. The data reconfirm our earlier published favorable preliminary results and support other studies that show a possible benefit of prenatal OSB repair on the urological outcome, but they also demonstrate that the positive effect remains limited.

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Urological Outcome after Fetal Spina Bifida Repair: Data from the Zurich Cohort

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Keywords

Bladder dysfunction · Fetal surgery · Myelomeningocele · Neuropathic bladder · Neurogenic bladder dysfunction · Spina bifida · Urodynamic studies · Urological outcome

Abstract

Introduction: Neurogenic lower urinary tract dysfunction (NLUTD) represents a severe burden for patients with open spina bifida (OSB). The effect of fetal OSB repair on the urological outcome remains unclear, as controversial data exist. The aim of this study was to further increment existing outcome data and to demonstrate that our earlier published positive preliminary results are not erratic. **Methods:** Data from standardized urological follow-up appointments of patients with fetal OSB repair operated at our center were analyzed. Data were obtained from urodynamic studies (UDSs) and radiologic exams performed in the newborn (gestational age 37–39 weeks), at ages of 6, 12, 18, and 24 months, and then at yearly intervals. **Results:** Of 82 patients (mean age 2.6 years, range 6 months to 7 years), 26 (32%) had a normal bladder function as demonstrated by UDSs. Of the 56 (68%) patients with NLUTD, 29 (51%) patients showed initially a normal UDS, but developed NLUTD in the follow-up, 19 (66%) of them spontaneously and another 10 (34%) in asso-

ciation with growth and development, or surgery of inclusion cysts. Radiologic abnormalities (upper tract dilatation and vesico-uretero-renal reflux) were seen in 15%, mainly patients with NLUTD. **Conclusion:** Our results add an important set of information to the existing body of evidence. The data reconfirm our earlier published favorable preliminary results and support other studies that show a possible benefit of prenatal OSB repair on the urological outcome, but they also demonstrate that the positive effect remains limited.

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Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) represents a severe burden for patients with open spina bifida (OSB). Although modern urological management allows preserving renal function in the majority of cases, it is only achieved with a negative impact on quality of life.

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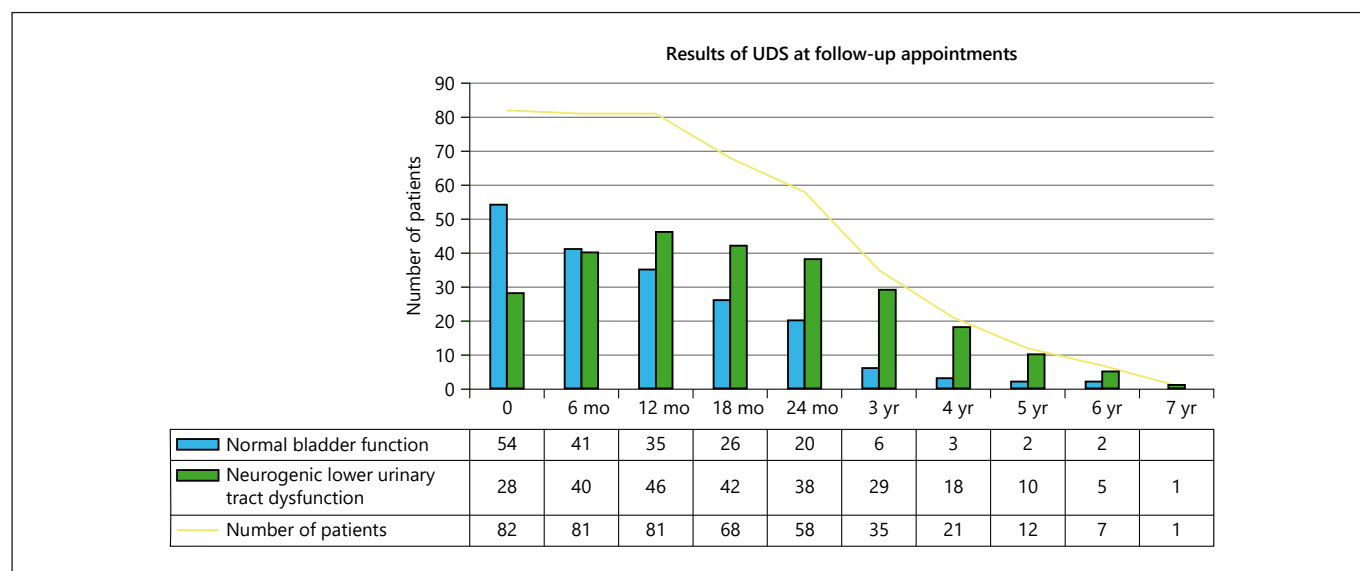


Fig. 1. Columns visualize the proportion of patients with normal bladder function to those with NLUTD at each follow-up appointments. The proportion becomes less representative in the older

age groups due to the decreasing number of patients. NLUTD, neurogenic lower urinary tract dysfunction; UDSs, urodynamic studies.

In the last years, in utero repair of OSB has become a treatment option for selected patients [1]. The rationale for in utero repair is the preservation of neurologic function by protecting the spinal cord from secondary damage during gestation [2]. While the MOMS trial demonstrated [3] (and our center delivered confirmative data [1]) that fetal OSB repair indeed is able to preserve neurologic lower extremity function and dramatically decreases rates of shunt-dependent hydrocephalus, the effect on the urological outcome remains unclear. Several studies on the urological outcome after in utero OSB repair were published [4–17], however reporting controversial results. The aim of this study was to further increment urological outcome data by analyzing our own cohort of patients who underwent in utero OSB repair, and to demonstrate that our earlier published positive preliminary results [7] are permanent.

Material and Methods

Data of 82 pediatric patients who underwent in utero OSB repair performed at the Zurich Center for Fetal Diagnosis and Therapy (www.swissfetus.ch) and who had at least a follow-up of 6 months were analyzed. The Zurich Spina Bifida Center provides a standardized follow-up for all patients operated at our institution, and follow-up data are collected prospectively using a registry created with REDCap. Urological follow-up exams include detailed history of micturition pattern, clean intermittent catheterization



(CIC), anticholinergic use, urinary tract infections (UTIs), urodynamic studies (UDSs), and renal ultrasound at all appointments. VCUG is obtained as baseline at the initial work-up and when clinically indicated.

We analyzed the data obtained from exams performed in the first 2 weeks of life (corrected for prenatal birth after a gestational age of 37 weeks), at 6, 12, 18, and 24 months, and then at yearly intervals. Further, history of postnatal spinal cord surgery was extracted from the registry. UDSs were performed in a standardized way according to the International Children's Continence Society [18] as described earlier elsewhere [7]. Based on micturition behavior and UDS findings, normal bladder was defined by the presence of a stable detrusor during filling, detrusor contraction leading to voiding, normal compliance, normal capacity for age, normal bladder sensation in older children, and no residual urine. Patients were treated according to current guidelines [19, 20].

Results

Eighty-two patients (mean age 2.6 years, range 6 months to 7 years, 59 females, 33 males) were analyzed. Twenty-six (32%) of these 82 patients showed a normal UDS at their last exam. In the newborn period, UDS was normal in 66% (54/82). At age 6 months, the UDS demonstrated in 51% (41/81) a normal bladder function. Of the patients who went through the first-year follow-up, 43% (35/81) had a normal bladder function, and of the ones who went through the second-year follow-up, 34% (20/58) had a normal bladder function. Thirty-five pa-

Patient number	Anatomical level	Functional level	Timepoints of follow-up urodynamic studies									
			Newborn	6 months	12 months	18 months	24 months	3 years	4 years	5 years	6 years	7 years
1	L3	L3										
2	L5	L5										
3	L4	L4										
4	L5	L5										
5	L3	S1										
6	L5	L5										
7	L4	S1										
8	T12	L5										
9	L2	L5										
10	L3	L3										
11	L4	L5										
12	L5	L3										
13	S1	S1										
14	S1	L5										
15	L4	L4										
16	L1	L3										
17	S1	L5										
18	L5	S1										
19	L5	L4										
20	L4	L4										
21	L5	L4										
22	L3	L4										
23	L3	L3										
24	L5	L5										
25	L3	L4										
26	L4	L4										
27	L5	L4										
28	L4	L4										
29	L4	L4										
30	L4	L4										
31	L4	L3										
32	S1	L5										
33	L4	L5										
34	L4	L4										
35	L4	L4										
36	L3	L4										
37	L5	L4										
38	L2	L5										
39	L5	L5										
40	L5	L4										
41	S1	L5										
42	L5	L5										
43	L5	L5										
44	L4	L4										
45	L5	L5										
46	T12	L4										
47	S1	L4										
48	L5	L5										
49	L3	L5										
50	L4	L5										
51	L2	L5										
52	L4	L4										
53	L4	L4										
54	L5	L4										
55	L5	L5										
56	T11	L4										
57	L3	L5										
58	S1	L5										
59	S1	L5										
60	L2	L4										
61	L3	L5										
62	L2	L4										
63	L5	L4										
64	S1	L5										
65	L4	L4										
66	S1	L5										
67	L5	L5										
68	L5	L5										
69	L4	L5										
70	L4	L5										
71	L3	L5										
72	L5	L5										
73	L1	L4										
74	L5	L5										
75	L5	L4										
76	L3	L5										
77	L4	L5										
78	L5	L4										
79	L5	L4										
80	L3	L5										
81	L5	L4										
82	L4	L4										

 Neurogenic lower urinary tract dysfunction
 Normal bladder function

tients had undergone the 3-year follow-up, and the percentage of patients with normal bladder function was 17% (6/35). The 3 patients who were older than 4 years and demonstrated a normal UDS voided volitionally with dry intervals. One of these 3 patients developed NLUTD after inclusion cyst resection and required thereafter CIC and anticholinergic medication (see below). Figure 1 depicts the number of patients who went through each follow-up exam and the distribution of patients with normal bladder and NLUTD.

The dynamics of neurourologic changes are illustrated in Figure 2. It lists all 82 patients in chronological order with the respective UDS results from each follow-up appointment. 23% (19/82) had initially a normal bladder function but showed in the follow-up a spontaneous deterioration to NLUTD (14 within the first 12 months, 4 between 12 and 18 months, and 1 between 18 and 24 months). Another 12% (10/82) developed NLUTD in association with inclusion cysts (at the mean age of 2.0 years, range 8–65 months). In 3.6% (3/82), neurourolog-

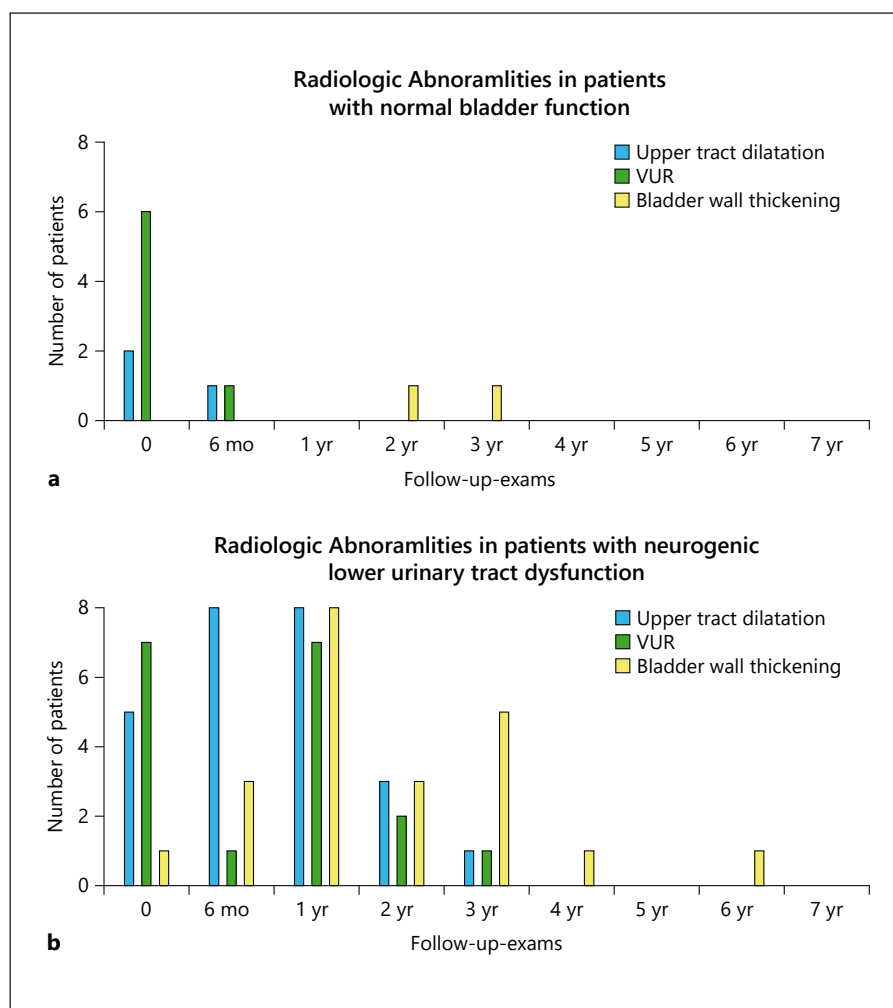


Fig. 3. a Patients with normal UDSs showed rarely radiologic changes such as upper tract dilatation, VUR, and bladder wall thickening. The diagram indicates numbers of patients at each interval found with radiologic changes. **b** In contrast to patients with normal UDSs (**a**), patients with NLUTD showed more frequently radiologic changes. NLUTD, neurogenic lower urinary tract dysfunction; UDS, urodynamic study; VUR, vesico-uretero-renal reflux.

Fig. 2. Dynamics of neurourologic changes. All patients are listed in chronological order with the respective UDS results from each follow-up appointment. Twenty-nine patients who had initially a normal UDS showed in the follow-up a NLUTD. The asterisks indicate neurosurgical resections of inclusion cysts. Note that of the 12 patients with resection of inclusion cysts, 7 had a normal bladder function up to the intervention, while in 3 patients, new occur-

rence of NLUTD prompted inclusion cyst resection. None of these 10 patients regained normal bladder function. The anatomic level in the table was retrieved from the first postnatal MRI and is defined by the first dysraphic vertebra. The functional level in the table is the first one diagnosed by a pediatric neurologist. The functional level may vary throughout the follow-up. NLUTD, neurogenic lower urinary tract dysfunction; UDS, urodynamic study.

Table 1. Summary of NLUTD treatments

Therapy of NLUTD (N = 56, 68%)	N	%
CIC only	12	14
CIC + anticholinergic therapy	42	51
+ Intradetrusor botulinum A toxin injection	7	8.5
Ureterocutaneostomy	1	1.2
Vesicostomy	1	1.2
Continence surgery (sling)	1	1.2

CIC, clean intermittent catheterization; NLUTD, neurogenic lower urinary tract dysfunction.

ic deterioration preceded diagnosis and neurosurgical resection of inclusion cysts. In 8.5% (7/82), NLUTD developed only after neurosurgical inclusion cyst resection; before surgery, the bladder function had been normal. None of these patients regained normal bladder function. One additional patient (1.2%) regained normal bladder function after cyst resection (at the age of 4.9 years) and after an initial period of spinal shock. Febrile urinary tract infections occurred in 27 patients (33%). All but 3 were patients with NLUTD.

The frequency of abnormal radiologic findings such as vesico-uretero-renal reflux (VUR), upper tract dilatation, and bladder wall thickening is reported in Figure 3a and b. These abnormalities mainly occurred in patients with NLUTD (Fig. 3b). Additional urological findings in our cohort were posterior urethral valves ($n = 1$), hypodysplastic kidneys ($n = 3$), and distal hypospadias ($n = 1$).

Treatment of NLUTD offered to our patients included CIC, anticholinergic therapy, and intradetrusor botulinum A toxin injection, ureterocutaneostomy, vesicostomy, and continence surgery. Details are reported in Table 1.

Discussion

The study presented here indicates that fetal OSB repair may have a positive effect on the lower urinary tract function, albeit limited. We found a higher percentage of patients with normal bladder function than percentages known from the literature after postnatal repair. In our cohort, 66% (54/82) newborns showed a normal UDS, while in newborns who had undergone postnatal OSB repair, UDSs were reported normal only in 12% [21] to 32% [22, 23]. Yet, a matter of concern is the finding that the percentage of normal bladder function decreases quite dramatically with time. In our cohort, the percentage of normal UDSs diminished from the mentioned 66%

(54/82) to 51% (42/82) at 6 months and 43% (35/81) at 1 year. Moreover, 23% (19/82) who had initially a normal bladder function developed spontaneously NLUTD during follow-up (74% in the first year). In addition, 12% (10/82) exhibited NLUTD in association with the development and surgery of inclusion cysts (at the mean age of 2.0 years). (We have reported earlier on the unexpectedly high occurrence of inclusion cysts after fetal OSB repair with loss of neurologic function [24].)

Changes in neurourologic status in the follow-up have also been described in patients with postnatal OSB repair. Sillén et al. [22] investigated infants with postnatal OSB repair urodynamically 3 times during their first year of life: changes in the urodynamic pattern occurred mainly in the first 4 months, and the main feature was an increase of detrusor activity, seen in 40% of the infants. Spindel et al. [25] noted neurourologic changes in 37% (29/79) of patients, usually occurring within the first 12 months, with 18% (15/79) showing deterioration. Nevertheless, despite the decreasing percentage of normal bladder function with age, we still found a higher number of patients with normal UDSs at older ages than patients with postnatal care. At the age of 3 years and older, 17% (6/35) of patients had normal UDSs. After postnatal OSB repair, normal bladder function was found in 5% of patients beyond the age of toilet training [26].

Radiologic abnormalities of the upper tract (upper tract dilatation and VUR) are aftermaths of unfavorable urodynamics (high-risk bladders with poor compliance, high leak point pressures, and hyperactivity), marking deterioration of the upper urinary tract [20, 22]. In our cohort, radiologic abnormalities (upper tract dilatation and VUR) were seen in 15% of the patients, and these were, as expected, mainly patients with NLUTD. This small percentage might indirectly support a positive effect of fetal OSB repair on the lower urinary tract. After postnatal OSB repair, hydronephrosis and VUR have been found in higher percentages (7–30% [27] and 20% [27] to 35% [22]). Sillén et al. [22] who diagnosed VUR in 35% (12/34) demonstrated the strong correlation between VUR and unfavorable urodynamics. However, in patients with postnatal OSB repair, upper tract dilatation may initially also be secondary to temporary urinary retention due to spinal shock.

Overall, in comparison to patients with postnatal OSB repair, the higher percentage of normal bladder function and low percentage of radiologic abnormalities found in our cohort across the different ages are promising. Our actual results confirm in part our short-term results published previously [7]. There, prospective comparison of 8

patients each with prenatal versus postnatal repair showed at age 2 years that only 50% of the prenatal surgery patients, but 100% of postnatal surgery patients, had lower urinary tract dysfunction ($p = 0.077$). The latter had also more bladder trabeculation and thicker bladder walls, while the former required significantly less CIC and anticholinergic medication.

Only few other studies described a positive urologic impact of fetal OSB repair. Carr et al. [6] reported on a 5-year follow-up of patients undergoing prenatal closure before the MOMS trial; 18.5% of fetal surgery patients demonstrated volitional voiding and continence, compared with 8.3% of patients in a historical group of postnatally repaired patients. Brock et al. [5] reported the results of the urological outcome in the MOMS patients (prenatal and postnatal surgery groups) in a first study published in 2015 [4] with data obtained at 30 months of age and in a second one published in 2019 with a mean follow-up of 7.4 years. In this last one, patients of the prenatal group showed more frequently spontaneous voiding (24 vs. 4%, $p < 0.001$) and required less CIC (62 vs. 87%, $p < 0.001$). Further, the prenatal group was on less bladder medication at the last follow-up. Interestingly, and in contrast to our study, videourodynamics or findings on renal/bladder ultrasound were, aside from a larger post-void residual urodynamic catheterization volume in postnatally operated patients, not statistically different. Pastuszka et al. [17] evaluated 36 patients with prenatal repair and 36 patients with postnatal repair, all treated at the same center with the same management after birth. As in Brock's study, but in contrast to our findings, urodynamics and imaging studies showed no differences between the groups. However, the authors concluded that prenatal OSB repair ensures statistically significant improvement of the degree of social urinary continence, reducing the risk of UTI and constipation.

On the other hand, several studies suggested little benefit of prenatal OSB repair concerning the urinary tract. The group of Macedo published several studies [12, 14, 15, 28, 29] of prospectively followed up patients with prenatal OSB repair and a high incidence of abnormal bladder patterns. In an analysis of 100 patients [15], only 15% showed a normal bladder profile at a mean age of 5.8 months (median 4 months). This low percentage strongly contrasts with the results of our cohort. Moreover, 5 other retrospective observational studies showed no significant improvements in lower urinary tract function after fetal OSB repair [8–11, 16]. However, these studies had serious limitations such as selection or treatment bias, the retrospective and non-controlled study design, and different outcome measurements.

The main limitation of the present study is that it is based prevalently on UDSs in infants and toddlers. Performing and interpreting UDSs in this age group is notoriously difficult as is comparison of results among studies. Also, only few patients are clearly beyond the toilet training period, and not only the rates of normal bladder function with normal urodynamic patterns but also volitional voids and dry intervals cannot be determined. Further, these older age groups are too small to draw conclusions. However, this study has the strength to analyze a large number of patients and to rely on a cohort with a standardized, almost gapless, prospective follow-up, done by a team of highly qualified and experienced examiners.

Future studies will have to reexplore the urological outcome when the cohort of children aged 6–7 years has become bigger. Other studies will have to investigate on which patients actually benefit from prenatal OSB repair and why, and on how these benefits can be further improved. In conclusion, we produce sound evidence for a clear-cut, but limited, benefit of prenatal OSB repair on urologic outcomes.

Acknowledgement

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Statement of Ethics

The study complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. The study was approved by our local Ethics Committee (KEK-ZH No. 2015-0172), and parents gave written informed consent.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

There were no funding sources for this study.

Author Contributions

L.M. designed the study, analyzed the data, and wrote the manuscript. A.H. obtained and analyzed the data and reviewed the manuscript. R.G., U.M., and M.M. discussed the data and reviewed the manuscript. M.H. designed the study, analyzed and discussed the data, and reviewed the manuscript.

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